# Protein

## At the centre of change in cirrhosis

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The Queen Elizabeth Hospital Birmingham Hepatology Department has extensive experience in optimising liver function. We have shown that specialist liver directed nutritional intervention plays a key role in reversing features of decompensated cirrhosis, such as jaundice, ascites, encephalopathy, and improving liver synthetic function, patient performance status and quality of life. In this article, we look at the key role of protein, the causes and impact of deficit and the potential corrective impact of protein optimisation as the lead nutrient in nutritional management of cirrhosis, including a case study demonstrating the improvements that are possible with specialist nutritional intervention.

## Malnutrition & liver cirrhosis

Malnutrition is a frequent complication of liver cirrhosis,[1] associated with the progression of liver failure with decompensation and a higher rate of complications.[2] Malnutrition with sarcopenia or sarcopenic obesity may worsen the prognosis of liver disease and lower survival. Early identification of the at-risk population with nutritional screening allows early nutritional assessment and management to preserve or optimise liver function and potentially reduce the risk of disease progression. It is recommended that patients who are at risk of malnutrition undergo a detailed nutritional assessment for the diagnosis and expert management of malnutrition.

Malnutrition is present in at least 50% of decompensated disease and more easily recognisable. However, there is a 20-40% presence of malnutrition in compensated disease, which is more challenging to identify but can impact liver function and increase the risk of decompensation.[3]

This requires expert dietetic assessment to identify subtle and significant changes in nutritional status impacting liver function.

Upper arm anthropometry, including mid arm circumference, triceps skinfold and mid arm muscle circumference, alongside handgrip measures, are completed as part of regular global dietetic assessment to identify muscle loss, reduced functional capacity and inform risk of decompensation.

Malnutrition is caused by numerous factors, such as: reduced intake, malabsorption, altered protein/energy metabolism and accelerated starvation.[4]

Altered metabolism of carbohydrates, fat and protein are one of the biggest contributing factors to malnutrition in cirrhosis.

Carbohydrate metabolism is impaired due to peripheral insulin resistance, hyperinsulinemia and impaired hepatic glycogen synthesis, resulting in poor hepatic glycogen stores and a state of accelerated starvation.

Alternate sources of rapid access energy are required in periods of short-term fasting approximately 2-3 hours after food, as there is no glycogen to draw against. Instead, muscle mass is broken down into amino acids for swift conversion to glucose as gluconeogenesis to supply background fuel between meals or during any non-food fuelled energy needs. Essentially there is muscle wasting in fed state[5] as a part of accelerated starvation.

This frequent muscle catabolism causes significant fatigue, muscle weakness and patients report often feeling 'hypo' and drained of energy.[4] This is also experienced by patients with compensated cirrhosis with early muscle loss, it is not confined to patients with decompensated disease.

Protein malnutrition leads to reduced substrate availability for muscle protein synthesis and thus plays an important role in physical frailty in patients with cirrhosis.

This is where protein optimisation steps in. As well as stripping protein from muscle mass, the body's protein pool is slowly depleted the longer the protein deficit exists. This can impact wound healing, skin regeneration, immune function and albumin synthesis.[5] The latter is impacted due to the reduced availability of protein as a source of synthesis. Hence the ongoing nutritional depletion of protein will impact the interpretation of albumin levels in cirrhosis. In this setting albumin levels can be interpreted as a red flag for increased protein uptake and insufficient availability of protein as a substrate for endogenous production on the background of accelerated starvation.

Additional fuel, such as fatty acids are needed to generate glucose. However, uptake of glycerol from lipolysis is reduced due to hepatic cellular dysfunction, resulting in myosteatosis. There is an increased usage of fat as an energy substrate overnight from approximately 40-50% of energy to 80-90% of energy.[6] After a twelve hour overnight fast patients with cirrhosis appear metabolically as a healthy individual would present after three days of starvation.

If we superimpose this protein void into the other factors that can cause malnutrition in liver disease, then the impact of this protein deficit gathers further force in driving decompensation in liver disease, as the protein gap widens with increased symptom burden, fatigue, muscle weakness and poor quality of life.

## Other factors influencing protein inadequacy

**Reduced oral intake:** Many causes including nausea, anorexia, early satiety, plus exhaustion and fatigue which will reduce volitional oral intake. Inappropriate dietary restrictions and frequent hospital admissions also play a part.[7]

**Malabsorption:** Malabsorption of fat as a result of biliary or pancreatic insufficiency will cause a nutritional deficit in both energy and protein, further impacting this protein void that will drive deterioration in both physical function and liver function. Biliary malabsorption is caused by a reduction of luminal bile acids secondary to decreased synthesis, and offering fat to levels of individual tolerance are recommended as best practice from our Centre. Lack of nutritional progression can be a red flag to question malabsorption in the setting of a climbing bilirubin and more obvious jaundice, particularly when supplements high in fat are being used as the treatment plan.[8, 9]

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Pancreatic insufficiency, in those with chronic alcohol consumption and widely in other liver disease aetiologies,[9,10] can occur independently without the presence of jaundice or concurrently with biliary malabsorption. Where jaundice is not present, it is evident that the existence of fat malabsorption is caused by pancreatic enzyme insufficiency. Our practice is to trial pancreatic enzyme replacement therapy and look for symptom response to minimise delay to optimal treatment.

**Ascites:** the build-up of fluid in the intrabdominal space, is caused by portal hypertension and retention of sodium and water. Ascites accelerates muscle loss through multiple pathways, including: gut malabsorption from portosystemic shunting,[11] protein loss via abdominal paracentesis, and the weight impact of fluid overload, which leads to physical frailty and reduced activity.

**Oedema:** is exacerbated by falling albumin synthesis. Our practice is to factor in a requirements for protein to support fluid management with adequate protein substrate to optimise albumin synthesis.

**Hepatic encephalopathy:** a state of neurocognitive and psychiatric dysfunction, results in a clinical state of fatigue, sleep disturbances and altered mental state, with patients reporting confusion, forgetfulness, poor motivation. The combination of these symptoms may further reduce oral intake. Protein catabolism is a driver of encephalopathy,[12] and there is a direct link between malnutrition and worsening encephalopathy. Muscle plays an important role in ammonia removal by increasing glutamine synthesis, a reaction that is catalysed by the enzyme glutamine synthetase.[13,14]

Preservation and increase in muscle mass to support the management of encephalopathy is key and is reliant upon sufficient provision of protein.

Protein breakdown and loss is at the core of the many symptoms of liver disease and provides us with a stronghold to be able to reverse the catabolic impact with the adequate and consistent provision of protein.

The protein requirements recommended in **Table 1** are based on a combination of the evidence base[15] and the best practice of our Team. We use requirements as a baseline and titrate according to anthropometric readings and clinical situation of the patient. Where there is lack of nutritional progression, we will escalate protein provision to support change. It is essential to accommodate additional protein needed due to losses, such as from ascites and malabsorption, or where there is an increased need with oedema, for example. We add in arbitrary increments of around 20-40 g additional per day to support progression.

We monitor biochemistry, renal function to look for excess and management of encephalopathy where protein provision is high.

**Table 1: Protein requirements**

| | g per kg estimated dry weight | Adjustments |
|---|---|---|
| Compensated | 1.2-1.5 g per kg | If BMI >30 use range from 75-100%. Compare to the patients usual intake and ensure increase. If BMI >40 use 65-100% as a range. |
| Decompensated | 1.5-2 g per kg<br>We provide >2 g per kg where losses are high and we are not seeing the improvement in functional capacity when muscle mass is stabilised with return of power or gain depending on our aims. | As above |

## Case Study

This case study of Mr H demonstrates the impact of liver decompensation as a driver of muscle loss and how this becomes self-perpetuating as muscle catabolism then acts as a driver for further decompensation. Reversing this process can support control and reversal of liver decompensation.

When protein needs are initially met and catabolism is prevented, the first feedback we have is from our patient reporting improved wellbeing. Halting muscle loss reduces fatigue, helps our patient feel better and can then improve volitional oral intake. However, it is rare that we can achieve adequate effective protein optimisation without the use of effective protein supplementation.

### Background & initial nutritional assessment

- Decompensated ALD cirrhosis. Abstinent
- Recent presentation with ascites and lower limb oedema – requiring large volume paracentesis
- Pitting oedema on legs
- PMH - T2DM diet controlled - Hba1c 33
- Moderate ascites – 6 litres – paracentesis due
- Wet weight: 94.85 kg; BMI 30.6 kg/m$^2$
- Normal weight: 95 kg; BMI 32 kg/m$^2$
- Reports some weight loss prior to fluid build up
- Reports thinning of the arms and legs recently
- Est dry weight ~84 kg; BMI 27 kg/m$^2$
- MAC: <25$^{th}$ by 0.4cm
- TSF: 25$^{th}$-50$^{th}$
- MAMC: - 25$^{th}$
- HGS: 25/24.8/20.6
- Function: Short walks and house actives, reports gets tired after ~1 hour
- Dietetic clinical impression: Significant loss of muscle and fat mass with reduced power due to accelerated starvation, prolonged fasting periods and ascitic losses. Active loss driving decompensation
- Estimated requirements:
  - Energy 30 kcal/kg/est dry weight = 2500 kcals.
  - Protein 2 g/kg/est dry weight = 168 g.

**Table 2** shows the progression of nutritional treatment and shows how the ascitic volume and oedema and albumin respond to protein optimisation alongside optimal medical management. Protein requirements are reduced as losses reduced from ascites and muscle is increasing.

This is accompanied by functional progression as protein requirements are consistently met and muscle mass is spared from catabolism. See **Figures 1-4**.

The anthropometry shows increasing mid arm circumference (MAC), small increase in triceps skinfold (TSF) and mid arm muscle circumference (MAMC), with concurrent increase in handgrip strength and physical function, directly in response to ongoing protein optimisation.

As Mr H's oral intake improved and calorie requirements were reducing, we changed to using Renapro® Shot as this offers a low energy, low carbohydrate bolus of 20 g protein, which supports protein supplementation only and does not further increase weight. Renapro® Shot and Renapro® powder are extremely effective in increasing muscle mass and allowing minimal weight gain where patients are of an acceptable body weight or are obese and need to remain weight neutral. Stand-alone protein products allow very high protein requirements to be met and are a critical part of optimal management for our patients. The nutritional management of cirrhosis is multifaceted but protein is at the heart. Protein requirements should be met as the pivotal first step to stabilise muscle mass and halt catabolism as the essential factor in supporting patient progression.

**Table 2: Patient progress**

| | July 2022 | September 2022 | November 2022 | January 2023 | March 2023 |
|---|---|---|---|---|---|
| Wet weight | 95 kg | 96 kg | 95 kg | 95 kg | 101 kg |
| Ascites | High volume with monthly paracentesis | High volume with monthly paracentesis | No further drains, ascites reducing | Minimal ascites | No ascites |
| Oedema | Pitting oedema to knee | Pitting oedema to knees | Mild oedema | Mild oedema | Mild ankle oedema |
| Estimated dry | 80 kg; BMI 26 | 78 kg; BMI 25 | 82 kg; BMI 27 | 88 kg; BMI 28 | 96 kg; BMI 32 |
| Protein requirement g/kg/est dry weight | 2 g per kg = 160 g | 2 g per kg = 160 g | 2g per kg = 170 g | 1.5-2 g = 130-170 g | 1.2-1.5 g = 90-120 g |
| Intake | Small meals, early satiety | Improved appetite meals eaten | Improved appetite meals eaten | Bigger portions, hungry, good appetite now | Eating meals and snacks |
| Supplements | Fortisip® Compact Protein x 4 per day – pt preference | Changed to Meritene® powder and Renapro® powder x 3 per day | Changed to Meritene® powder and Renapro® powder x 3 per day | Change to Meritene® powder and Renapro® powder x 3 per day | Changed to Renapro® Shots to reduce energy provision |
| Nutritional provision | 1200 kcal 72 g protein | (semi skim milk) 900 kcal 105 g protein | (semi skim milk) 900 kcal 105 g protein | (semi skim milk) 900 kcal 105 g protein | 300 kcal and 60 g protein |

**Figure 1: Protein – The key to achieving change in chronic liver disease**

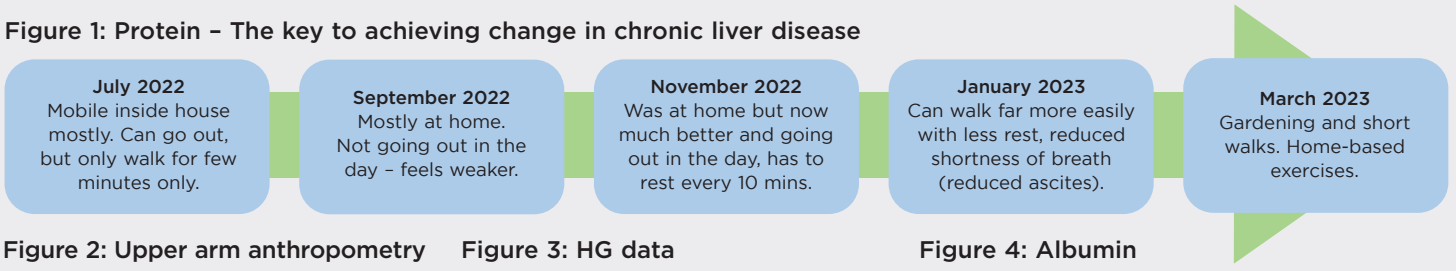



**Figure 2: Upper arm anthropometry**

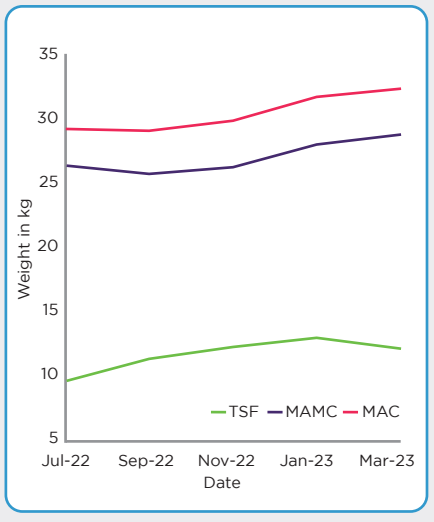



**Figure 3: HG data**

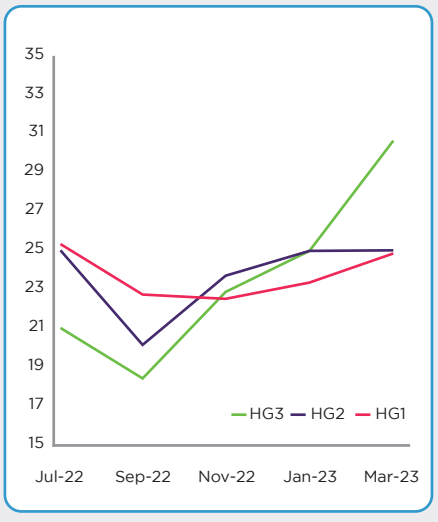
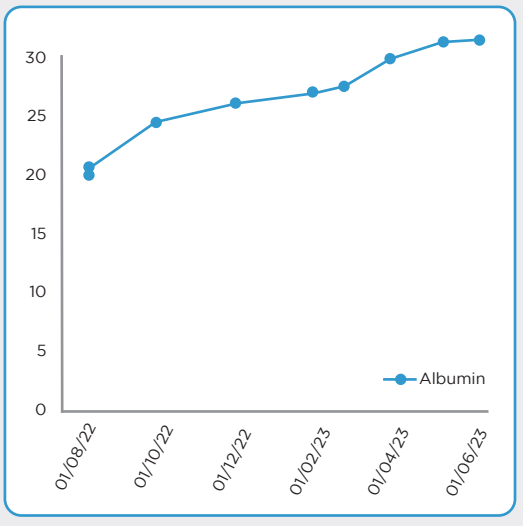



**Figure 4: Albumin**

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